# Efficacy of a Vancomycin Solution to Prevent Bacteremia Associated With an Indwelling Central Venous Catheter in Neutropenic and Non-Neutropenic Cancer Patients

**Francisco J. Barriga, MD,[1]* Monica Varas, MD,[1] Marcela Potin, MD,[1] Francisco Sapunar, MD,[2] Hector Rojo,[3] Alejandro Martinez,[3] Veronica Capdeville, RN,[1] Ana Becker, MD,[4] and Pablo A. Vial, MD[1]**

We evaluated the efficacy of a vancomycin solution in the prevention of bacteremia caused by vancomycin-sensitive organisms (VSO) in cancer patients with a tunneled central venous catheter (CVC). Eighty-three patients who had a single lumen CVC were randomized to use a heparin solution (25 U/ml) for daily catheter flush with (HepVan) or without (Hep) vancomycin, 25 mcg/ml. Febrile episodes were recorded, and central and peripheral blood cultures were drawn before beginning antibiotic therapy. Patients participated in follow-up for 16,677 catheter days (8,666 Hep and 8,011 HepVan), and 143 febrile episodes were recorded (82 Hep and 61 HepVan). Forty-four episodes of bacteremia occurred, 23 of them due to VSO (16 occurred in the Hep group and 7 in the HepVan group ($P = 0.19$). VSO bacteremia occurred in 14 neutropenic (absolute neutrophil count $< 500 \times 10^9$/l) episodes (7 Hep vs. 7 HepVan) and in 9 non-neutropenic episodes (9 Hep vs. 0 HepVan; $P = 0.013$). Vancomycin effectively prevented bacteremia by VSO in non-neutropenic patients, supporting the idea that intraluminal colonization of indwelling CVCs contributes to bacteremia only in these patients. **Med. Pediatr. Oncol. 28:196–200** © 1997 Wiley-Liss, Inc.

**Key words:** central venous catheter; bacteremia; prevention

## INTRODUCTION

The use of indwelling central venous catheters (CVC) has become widespread in cancer patients, both in children and adults [1]. They allow the safe administration of chemotherapy and other intravenous infusions and prevent painful needle punctures. Their use is associated with known risks, among which local infection and primary bacteremia are the main causes of morbidity [2]. Primary bacteremia is potentially the most harmful complication because of the immunocompromised state of cancer patients. Making CVC use safer by preventing bacteremia has been the subject of recent studies [3,4], the results of which have been controversial. Based on the observation that vancomycin can be stable in a heparin solution for long periods [5], Schwartz et al. [3] reported a significant reduction in bacteremia due to vancomycin-sensitive organisms (VSO) by adding the antibiotic to a heparin flush solution in a group of 45 children with tunneled CVCs. This study stratified the patients according to the intensity of therapy before randomization. Rackoff et al. [4] reported the results of another randomized trial including 55 pediatric cancer patients with tunneled CVCs. There was not difference in the rate of bacteremia attributable to luminal colonization in the group using prophylactic vancomycin.

There is no consensus to define a catheter-associated bacteremic episode. This lack of definition particularly applies to cancer patients when the episode occurs during a period of neutropenia. In this situation, other possible sources of bacteremia are likely, such as breakdown of gastrointestinal tract barriers and chemotherapy-induced mucositis [6]. It could be hypothesized that because of this, the role of the CVC in the pathogenesis of bacteremic episodes would be more prevalent in non-neutropenic patients. Recent studies of vancomycin prophylaxis to prevent coagulase-negative staphylococcal bacteremia in premature neonates with CVCs, who although immune deficient are non-neutropenic, have supported this hypothesis [7–9]. Thus, the efforts to prevent these infections in cancer patients by the use of prophylactic intraluminal antibiotics would be effective only during periods when the patient is non-neutropenic, and prophylaxis would offer a very modest benefit to patients using it. Neither of the bacteremia prevention trials in these patients addressed the issue of neutropenia in the episodes

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[1]Departments of Pediatrics and [2]Hematology, Pontificia Universidad Catolica de Chile; [3]Formulario Nacional; [4]Department of Pediatrics, Hospital Sotero Del Rio, Santiago, Chile.

*Correspondence to: Francisco Barriga, MD, Pontificia Universidad Catolica de Chile, Marcoleta 367, P.O. Box 114-D, Santiago, Chile.

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they reported. A secondary concern of the long-term use of low-dose prophylactic antibiotics is the possible selection for resistant flora [10,11], an occurrence particularly worrisome with Gram-positive organisms that, after becoming resistant to vancomycin, have few other therapeutic options.

To test the hypothesis that intraluminal colonization of tunneled CVCs contributes to bacteremia only in non-neutropenic patients using such devices, we embarked on a prospective, randomized, double-blind trial performed at two institutions treating cancer patients, mainly in the pediatric age group. The objective of our study was to compare the efficacy of vancomycin in preventing bacteremia caused by VSO in neutropenic and non-neutropenic patients. A significant reduction of bacteremic episodes in non-neutropenic patients coupled with no effect in neutropenic patients would lend strong support to our hypothesis.

## PATIENTS AND METHODS

### Patient Population and Randomization

Patients with various malignancies who had a single lumen Hickman Broviac (Bard Access Systems, Salt Lake City, UT) catheter and were treated at two institutions in Santiago, Chile, were enrolled in this trial from May 1991 to February 1994. The patients or the parents were asked to sign a consent form, and they were given standardized CVC care instructions by the same nurses. They were randomized to use a heparin (Organon Teknika, The Netherlands) solution of 25 U/ml for daily CVC flush with (HepVan group) or without (Hep group) vancomycin, 25 mcg/ml (Lyphomed, Rosemont, IL). The solutions were prepared in batches of single-use, 5-ml ampules, and each batch was tested for bacterial contamination before distribution. The patients were randomized to one of four color-coded groups of ampules—two that had vancomycin and two that did not. All investigators, except for the ones responsible of the preparation of heparin/vancomycin ampules, were blinded to the contents of them. Patients received a new batch every 60 days, at which time they turned in any remaining ampules. The vancomycin contents of the ampules were blinded to all investigators and caretakers.

### Febrile Episodes

All febrile episodes were documented in participating patients during the observation period. An independent febrile episode was recorded when the patient was ambulatory and had at least one axillary temperature measured at or above 38.5°C. All patients were hospitalized, and a complete blood count as well as central and peripheral blood cultures were obtained and processed in supplemented tryptic soy broth with SPS (BacT/Alert Microbial Detection Systems, Organon Teknika, Durham, NC). Patients then began receiving broad-spectrum antibiotics. Neutropenic patients (absolute neutrophil count $< 500 \times 10^9$/l) received ceftazidime and amikacin, and non-neutropenic patients received cloxacillin and amikacin, based on the relatively high incidence of oxacillin-sensitive staphylococci strains in our patient population [12]. Each hospitalization was considered a single febrile episode irrespective of the temperature evolution. Recurring fever at least 72 hours after hospital discharge, with the patient taking no antibiotics was considered a separate febrile episode.

### Definition and Management of Bacteremia

Bacteremia was defined as the presence of at least one positive blood culture obtained from the CVC or peripheral blood at the time of initial evaluation. Patients with positive blood cultures received a full 10- to 14-day course of antibiotics. Neutropenic patients were maintained with broad-spectrum coverage until resolution of neutropenia. Non-neutropenic patients received therapy according to culture sensitivity. When blood cultures were reported negative, antibiotics were stopped in non-neutropenic patients after 48 hours and in neutropenic patients after resolution of neutropenia.

### Statistical Analysis

Sample size estimates were based on our previous study of infectious complications associated with permanent CVC use in cancer patients [12]. In that study, 48 patients with tunneled CVCs underwent follow-up for 9,506 catheter days (average, 198 catheter days per patient). A total of 122 febrile episodes occurred, 44 of them (36%) associated with bacteremia and 19 with VSO bacteremia. Of these, 13 (10.6%) were in non-neutropenic patients. We assumed that in a similar population of cancer patients, the same proportion of febrile and bacteremic episodes would occur, given that a comparable number of catheter days are followed. The addition of vancomycin would reduce the incidence of VSO bacteremia in non-neutropenic patients from a maximum of 15% to less than 2% of the episodes. The incidence of VSO bacteremia in neutropenic patients would remain unchanged. Given this assumption, 60 febrile episodes in each group were needed to show, with a 95% certainty, that a difference exists and to have 80% power. We thus aimed to include 40 patients in each group, expecting to reach the desired number of catheter days and febrile episodes. We chose this approach based on the assumption that cancer patients participating in follow-up for a long period have independent episodes of fever and catheter-related bacteremia that may or may not be prevented with the use of prophylactic vancomycin.

In each group, we compared the proportion of febrile episodes in neutropenic and non-neutropenic patients, the proportion of bacteremic episodes caused Gram-positive

**TABLE I. Distribution of Participating Patients Among the Hep and HepVan Groups by Diagnosis and Total Number of Catheter Days**

| | Hep | HepVan |
|---|---|---|
| No. of Patients | 44 | 39 |
| Acute lymphoblastic leukemia | 31 (70%) | 24 (61%) |
| Acute nonlymphoblastic leukemia | 4 | 1 |
| Lymphoma | 2 | 5 |
| Neuroblastoma | 3 | 2 |
| Sarcoma | 3 | 4 |
| Brain tumors | 0 | 2 |
| Hepatoblastoma | 1 | 1 |
| Catheter days | 8,666 | 8,011 |
| Average CVC placement in days (range) | 196 (16–571) | 205 (7–685) |

CVC = central venous catheter.

(VSO) and other organisms, and the proportion of bacteremia caused by VSO in neutropenic and non-neutropenic patients. The analysis was done with the chi-square test, alternatively using the Fisher exact test when appropriate.

## RESULTS

### Patients

Eighty- three patients participated in this trial. There were 38 females and 46 males (age range, 2–55 years; median age, 6 years). Six patients were older than 20 years. Fifty-nine patients had the diagnosis of acute lymphoblastic leukemia, 13 other hematologic malignancies, and 11 solid tumors. Seventy-six patients entered the study on insertion of the CVC, and 7 were included from 2 to 10 months after insertion. Forty-four patients were randomized to the Hep group, and 39 patients to the HepVan group (Table I). The groups were comparable in number of patients, distribution of patients by diagnosis, and average length of catheter placement. Patients underwent follow-up for 16,677 catheter days during the study period (8,666 Hep and 8,011 HepVan).

### Febrile Episodes

We recorded 143 febrile episodes in 64 patients (82 in the Hep group and 61 in the HepVan group). Nineteen patients had no febrile episodes, 25 patients had one episode, 19 patients had two episodes, and 20 patients had three or more episodes. Patients with more than one febrile episode had a median of 38 days between them (range, 6–536 days). Ninety-four episodes occurred in neutropenic patients (47 Hep and 47 HepVan), and 49 episodes occurred in non-neutropenic patients (35 Hep and 14 HepVan, $P = 0.014$).

### Bacteremic Episodes

Bacteremia was detected in 44 of 143 febrile episodes. Gram-positive organisms were found in 23 episodes, and gram- negative organisms were found in 20 (Table II). *Staphylococcus epidermidis* and *Escherichia coli* were the most frequent isolates (29.5% and 22.7%, respectively). There was one episode of Candida. Positive blood cultures were obtained from the CVC alone in 24 cases, from both central and peripheral samples in 13 cases, and from peripheral blood samples alone in 7 cases. Of the latter, three were due to VSO. Only three patients had two separate bacteremic episodes caused by the same organism separated by 23, 34, and 85 days, respectively. Twenty-six episodes of bacteremia were registered in the Hep group and 18 in the HepVan group (Table III). Twenty-three episodes were due to VSO, 16 (19.5%) in the Hep group and 7 (11%) in the HepVan group ($P = 0.19$). Fourteen episodes of VSO bacteremia occurred in neutropenic patients (seven Hep and seven HepVan), and nine occurred in non-neutropenic patients. All nine (11%) occurred in the Hep group, with no episodes in the HepVan group ($P = 0.019$, Table III). Seven patients accounted for these nine episodes. In two patients, a second bacteremic episode occurred while non-neutropenic, separated 34 and 85 days from the first one, respectively.

Vancomycin-resistant Gram-positive organisms were not found. We had no episodes of deep fungal infections in this study population, although a single episode of candidemia was recorded. There were seven episodes of exit site infection during the study (0.41 per 1,000 catheter days).

## DISCUSSION

Bacteremia is a frequent complication of CVC use. It can be a potentially dangerous condition in neutropenic cancer patients that can result in hospitalization, the use of broad-spectrum antibiotics, and delays in cancer therapy. We evaluated the efficacy of a vancomycin solution in the prevention of bacteremia in cancer patients with a tunneled CVC, comparing neutropenic versus non-neutropenic episodes. Our definition of bacteremia in the study group was purposefully broad (at least one positive blood culture) for the following two reasons.

**TABLE II. Bacterial Isolates in 44 Bacteremic Episodes in Patients in the Study and Their Distribution Among the Study Groups**

| | No. | % | Hep | HepVan |
|---|---|---|---|---|
| Gram positive (VSO) | | | | |
| *Staphylococcus epidermidis* | 13 | 29.5 | 8 | 5 |
| *Staphylococcus aureus* | 6 | 13.6 | 4 | 1 |
| *Streptococcus viridans* | 2 | 4.5 | 1 | 1 |
| *Streptococcus pneumoniae* | 1 | 2.2 | 1 | 0 |
| Group D Streptococcus | 1 | 2.2 | 1 | 0 |
| Gram negative and others | | | | |
| *Escherichia coli* | 10 | 22.7 | 4 | 5 |
| Klebsiella spp. | 5 | 11.3 | 3 | 2 |
| Enterobacter spp. | 3 | 6.8 | 2 | 1 |
| Salmonella spp. | 1 | 2.2 | 1 | 0 |
| *Pseudomonas aeruginosa* | 1 | 2.2 | 0 | 1 |
| *Candida albicans* | 1 | 2.2 | 0 | 1 |

VSO = vancomycin-sensitive organisms.

**TABLE III. Comparison Between Febrile and Bacteremic Episodes due to VSO Among the Study Groups**

| | Hep (%) | HepVan (%) | *P* value |
|---|---|---|---|
| Febrile episodes | 82 (100) | 61 (100) | |
| Neutropenic | 47 (57.3) | 47 (77) | |
| Non-neutropenic | 35 (42.7) | 14 (23) | 0.014* |
| Bacteremic episodes (VSO) | 16 (19.5) | 7 (11.4) | 0.19* |
| Neutropenic | 7 (8.5) | 7 (11.4) | 0.55* |
| Non-neutropenic | 9 (10.9) | 0 (0) | 0.01** |

VSO = vancomycin-sensitive organisms.
*Chi-square test.
**Fisher exact test.

1. It is standard medical practice to draw blood cultures in all cancer patients who are febrile and have a CVC and to treat them with broad-spectrum antibiotics before culture results are known. A single positive blood culture in these patients, even with coagulase-negative staphylococci, usually warrants a 10-day course of antibiotics [13,14].
2. There is no overall agreement as to what constitutes a real CVC-related episode of bacteremia versus contamination of the culture sample, even when positivity differs between central and peripherally obtained cultures and techniques such as differential colony count are used [14–18].

We followed the same methodology reported by Schwartz et al. [6] in the preparation of heparin and vancomycin, except for the use of single-dose ampules without rubber caps. Patients underwent follow-up for 16,677 catheter days, during which 143 febrile episodes, 44 episodes of bacteremia, and 23 episodes of VSO bacteremia occurred. The randomization groups were comparable in the distribution of patients' diagnosis and therapy. Acute lymphoblastic leukemia was overrepresented as the most common childhood malignancy. The overall incidence of bacteremia was similar to that reported in many studies [19–22]. We found no difference in the incidence of VSO bacteremia between the two groups as a whole, but a significant difference was found when the episodes were separated in neutropenic and non-neutropenic. Our analysis differed from the previous published reports [3,4] in that we compared febrile and bacteremic episodes among the study groups, even if some of the participating patients had more than one episode.

These results indicate that intraluminal colonization of the CVC with microorganisms as a cause of bacteremia can be prevented by the use of low-dose antibiotics. However, this measure is ineffective during periods of neutropenia, when the patient can and will be exposed to infection through many other possible routes, mainly the gastrointestinal tract. Therefore, the results support the theory that the role of intraluminal colonization of the CVC is important in bacteremic episodes only in non-neutropenic patients.

We also found a significant difference in the number of febrile episodes in non-neutropenic patients among both groups. A possible explanation for this could be that

VSO infections not detected by a single blood culture, which are effectively prevented by the addition of vancomycin, occurred in this group of patients. Because all patients received a 48-hour course of antibiotics until the results of the cultures were known, it could be possible that some of these undetected episodes were effectively treated by this short course of antibiotics.

## CONCLUSIONS

Our results support the following practical considerations.

1. Vancomycin in the heparin flush solution can be used to prevent bacteremia by VSO organisms in patients with CVCs, but this measure will be of modest benefit to cancer patients treated with intensive chemotherapy protocols. As alluded to above, this practice has to be weighed against the risk of selecting for resistant flora.
2. When CVC removal can be avoided, bacteremia therapy in non-neutropenic patients could be simplified by administering full-dose antibiotics until defervescence and then continuing daily or twice daily administration to eradicate CVC colonization. Nevertheless, the safety of this practice would have to be supported by a well-designed comparative trial [13,23].

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